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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,792	MARGOLSKEE ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-16 and 18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendments filed 3-4-04 (with changes to the sequence listing in paper and CRF form), 7-12-04 and transmittal of color drawings of 8-11-04 have been entered into the record and have been fully considered.

2. Estacion et al., and Okada et al., are removed as prior art in view of the amendment to the claims directing the structural limitation of SEQ ID NO:4.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. The 112 2nd paragraph rejection of record is withdrawn in view of Applicant's arguments that the skilled artisan would know suitable assays for assessing activation and inhibition of TRP8 as established in the prior art. This argument is persuasive as evidenced by the prior art newly cited as necessitated by amendment (the claims are newly drawn to TRP8 of SEQ ID NO:4, see Zucker et al., 102(e) US 2002/0164645). Zucker establishes suitable measurements for TRP8 activation and inhibition of taste receptor cell responses including for salty, sour, bitter and sweet sensations as well as methods for assessing compounds that modulate, activate and inhibit such taste signaling responses. Applicant's are placed on notice that obviation of the new matter rejection set forth herein will remove Zucker from the available prior art of record, and thereby remove the basis for withdrawal of the 112, second paragraph rejection of record. In this case, the rejection may be reinstated absent further evidence within the piror art that establishes well known assays for the assessment of TRP8 activation and/or inhibtion and how such correlates to the perception of a bitter as opposed to a

sweet taste. While applicants have argued that such is within the skill of the art, no such evidence was presented in Applicant's response and the only such evidence/relevant reference found by the examiner is Zucker, now cited and relied upon for withdrawal of the rejection.

5. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the examiner.

6. Claims 1-23 are pending.

Sequence Compliance

7. The noted corrections within the sequence listing and CRF form are supported within the priority application and within the instantly filed original figures which appear to be poor photocopies of the original provisional application pages. The amended drawings submitted 10-31-02 are good copies and refer to the sequences therein by SEQ ID NO:. The corrections to the paper copy and CRF place the case in proper sequence compliance and correct the inadvertent errors in the sequence listing and CRF form.

Drawings

8. Applicants have stated that they wish to use the color drawings for examination purposes only.

Election/Restriction

9. Applicant's election with traverse of Group IV, to the extent of human TRP8 of SEQ ID NO:4, claim 17 in Paper No. 14 submitted 3-24-03, is acknowledged. The traversal is on the ground(s) that the claimed processes of Groups I-X are not

independent and distinct as required by 35 USC 121. This is not found persuasive because as set forth in the restriction requirement of 2-25-03 the products and methods are distinct as claimed and directed to divergent compounds, steps, effects and outcomes. A search for any one product or method is not co-extensive with any other and search and examination of the multiple groups in a single application bears undue burden upon the Examiner.

The requirement is still deemed proper and is therefore made FINAL

10. Claims 1-16, and 18-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicants note that, "Claim 17 has been amended and now clearly and distinctly recites a method for identifying a compound that induces or inhibits the perception of a

bitter taste by the activation or inhibition of TRP8. The method of Claim 17 comprises the contacting of a cell, expressing the human TRP8 channel protein of SEQ ID NO: 4, with a test compound and measuring the level of TRP8 activation and comparing the level of activation to a vehicle control. Claim 17 as presently amended has written descriptive support as described in the Specification, inter alia. at page 15, lines 20, to page 17, line 6, and in Example 6.2.5, page 32-33. Specifically. see page 10, lines 22-27, and page 16, lines 28-30.

The examiner notes that the page citations referenced are apparently off by several pages. It is believed that applicants have intended to refer the examiner to the screening assays at pp. 20-22, Example 6.2.5 at pp. 42-43. Applicants reference to p. 10 and 16 remains unclear to the examiner as to support for the newly recited assay as directed to inducrs and inhibitiors and the measurements of neurtral and decreased levels of activatio of TRP8 as claimed. Review of the specification by the examiner notes support for assays as at p. 20-22. However, these assays apparently differ in that when the assay is to define an inhibitor the assays are noted to be performmed in the presence of a test compound and a bitter tastant. Moreover, no support is found for the recitation where the change is deemed a neutral level of activation as recited. Thus, the recitations constitute new matter absent written description support from the specification as originally filed. Support is noted for the assay as directed to measuring the level of activation in the presence of a test compound and the indication of a TRP8 activator. These noted deficiencies are shared with the priority document of 60/197,491. Thus, the newly claimed method lacks sufficient support from the priority document to obtain full benefit of an earlier filing date under 35 USC 119(e). This rejection is necessitated by Applicant's amendment to the claims (3-4-04).

13. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro assays via contacting isolated cells, does not reasonably provide enablement for cells as generically recited which read on transgenic animals and gene therapy approaches. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The specification speaks of in vitro and in vivo assays. Also contemplated are transgenic animals, and methods of gene therapy whereby cells are manipulated for expression of TRP8 as well as both in vitro and in vivo assays within such cells and whole animal organisms, including humans.

While the specification is enabling for contact with isolated cells, and the transformation or transfection of isolated cells to express TRP8 protein via nucleic acid and vector delivery, the specification fails to teach suitable administration such that any suitably transgenic, transformed or gene vector therapy administered organism may be suitably screened. What is lacking is a description of the proper construct and transformation or transfection procedures as well as mechanisms for assessing TRP8 activation in vivo, including in humans and in transgenic humans as encompassed by

the claims. Those skilled in the art recognize that such technology is currently beyond scope. In particular, Marshall "Gene Therapy's Growing Pains". Science, Vol. 269 (1995), pp. 1050-1055, Orkin et al. "Report and recommendations of the panel to assess the NIH investment in research on gene therapy". (1995). pp. 1-25, and Verma, I. M., et al. "Gene therapy-promises, problems, and prospects". Nature, Vol. 389 (September 1997), pp. 239-242, each denote significant troubles associated with transgenic and in vivo gene therapy approaches to the assessment of in vivo methods and treatments.

The specification fails to provide any exemplary evidence for conducting such screening approaches in vivo, using either transgenic or gene therapy treated cells within an organism. Since the scope of "cell" is deemed to be so inclusive as provided by direct guidance within the specification, the scope of enablement provided by the specification is not commensurate in scope with the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation. Amendment to "isolated" cells is recommended.

Priority

14. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

As noted above in the new matter rejection, support is not found for the newly amended claim recitations, either within the priority application or instant specification. Accordingly the effective filing date of claim 17 is the date of instant filing (4-13-01) absent full support within the priority application. Prior art is cited accordingly. This determination is necessitated by Applicant's amendment of the claims (3-4-04).

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claim 17 is rejected under 35 U.S.C. 102(e) as being anticipated by Zucker et al., US 2002/0164645 published Nov. 7, 2002 with benefit of priority to Dec. 29, 2000.

Zucker et al., teach claims 1-4 directed to screening assays for compounds that

modulate taste receptor signaling as particularly noted below:

1. A method for identifying a compound that modulates taste signaling in taste cells, the method comprising the steps of: (i) contacting the compound with a eukaryotic host cell or cell membrane which expresses a taste cell-specific ion channel subunit: (a) having greater than about 70% amino acid sequence identity to a polypeptide having a sequence selected from the group that consists of SEQ ID NO: 2, SEQ ID NO: 5, and SEQ ID NO: 8; and (b) specifically binding to polyclonal antibodies that specifically bind to a polypeptide having a sequence selected from the group that consists of SEQ ID NO: 2, SEQ ID NO: 5, and SEQ ID NO: 8; and (ii) determining a functional effect of the compound upon a transmembrane ion flux of a predetermined ion, thereby identifying a compound that modulates taste signaling in taste cells.
2. The method of claim 1, wherein the functional effect is determined by measuring changes in intracellular ion concentration.
3. The method of claim 1, wherein the functional effect is determined by measuring changes in intracellular Ca.sup.++.
4. The method of claim 1, wherein the changes in ion flux are measured by an assay selected from the group consisting of a voltage clamp assay, a patch clamp assay, a radiolabeled ion flux assay, or a fluorescence assay using ion sensitive dyes.

Zucker also specifically notes:

Detail Description Paragraph:[0024] The invention provides methods of screening for modulators, e.g., activators, inhibitors, stimulators, enhancers, agonists, and antagonists of TC-ICS.

Zucker also notes as follows:

Summary of Invention Paragraph:[0009] Elucidating the mechanisms of taste cell signaling and information processing are critical for understanding the function, regulation, and "perception" of the sense of taste. Although much is known about the psychophysics and physiology of taste cell function, very little is known about the molecules and pathways that mediate these sensory signaling responses (reviewed by Gilbertson, Current Opn. in Neurobiol. 3:532-539 (1993)). Electrophysiological studies suggest that sour and salty tastants modulate taste cell function by direct entry of H.sup.+ and Na.sup.+ ions through specialized membrane channels on the apical surface of the cell. In the case of sour compounds, taste cell depolarization is hypothesized to result from H.sup.+ blockage of K.sup.+ channels (see, e.g., Kinnamon et al., PNAS USA 85: 7023-7027 (1988)) or activation of pH-sensitive channels (see, e.g., Gilbertson et al., J. Gen. Physiol. 100:803-24 (1992)); salt transduction may be partly mediated by the entry of Na.sup.+ via amiloride-sensitive Na.sup.+ channels (see, e.g., Heck et al., Science 223:403-405 (1984); Brand et al., Brain Res. 207-214 (1985); Avenet et al., Nature 331:351-354 (1988)). Most of molecular components of the sour or salty pathways have not been identified.

Summary of Invention Paragraph:[0010] Sweet, bitter, and unami transduction are believed to be mediated by G-protein-coupled receptor (GPCR) signaling pathways (see, e.g., Striem et al., Biochem. J. 260:121-126 (1989); Chaudhari et al., J. Neuros. 16:3817-3826 (1996); Wong et al., Nature 381:796-800 (1996)). Confusingly, there are almost as many models of signaling pathways for sweet and bitter transduction as there are effector enzymes for GPCR cascades (e.g., G protein subunits, cGMP phosphodiesterase, phospholipase C, adenylate cyclase; see, e.g., Kinnamon & Margolskee, Curr. Opin. Neurobiol. 6:506-513 (1996)). Identification of molecules involved in taste signaling is important given the numerous pharmacological and food industry applications for bitter antagonists, sweet agonists, and modulators of salty and sour taste.

Summary of Invention Paragraph:[0012] The present invention demonstrates, for the first time, taste cell-specific expression of nucleic acids encoding an ion channel subunit. The taste cell-specific ion channel subunits that are specifically expressed in taste cells can thus be used to screen for modulators of taste cell function and to control taste perception. The compounds identified by these assays would then be used by the food and pharmaceutical industries to customize taste, e.g., as additives to food or medicine so that the food or medicine tastes different to the subject who ingests it. For example, bitter medicines can be made to taste less bitter, and sweet substance can be enhanced.

Detail Description Paragraph:[0026] These nucleic acids and proteins also provide valuable probes for the identification of taste cells, as the nucleic acids are specifically expressed in taste cells. For example, probes for TC-ICS are used to identify subsets of taste cells such as foliate cells and circumvallate cells, or specific taste receptor cells, e.g., sweet, sour, salty, and bitter. They also serve as tools for the generation of taste topographic maps that elucidate the relationship between the taste cells of the tongue and taste sensory neurons leading to taste centers in the brain. Furthermore, the nucleic acids and the proteins they encode are used as probes to dissect taste-induced behaviors.

Detail Description Paragraph:[0088] Ion channel modulation typically initiates or inhibits subsequent intracellular events via, e.g., G-proteins and/or other enzymes, such as adenylate cyclase or phospholipase C, which are downstream from the ion channel-mediated events in taste transduction pathways. For example, ion channel activation may result in a change in the level of intracellular cyclic nucleotides, e.g., cAMP or cGMP, by activating or inhibiting enzymes such as adenylate cyclase by G-protein .alpha. and .beta..gamma. subunits. These intracellular cyclic nucleotides, in turn, may modulate other molecules, such as, cyclic nucleotide-gated ion channels, e.g., channels that are made permeable to cations by binding of cAMP or cGMP (see, e.g., Altenhofen et al., Proc. Natl. Acad. Sci. U.S.A. 88:9868-9872 (1991) and Dhallan et al., Nature 347:184-187 (1990)). Cells for this type of assay are made by co-transfection of a host cell with any one or a combination of DNA encoding a cyclic nucleotide-gated ion channel, GPCR phosphatase, DNA encoding TC-ICS, and DNA encoding a G-protein coupled receptor. The receptor may be, e.g., metabotropic glutamate receptors, muscarinic acetylcholine receptors, dopamine receptors, serotonin receptors, and the

like, which, when activated, causes a change in cyclic nucleotide levels in the cytoplasm.

Thus, Zuckers method of assessing compounds that modulate taste signaling in taste cells anticipates the steps of instant claims. Zucker notes the assessment of bitter taste and in response to activation or inhibition of SEQ ID NO:8 bearing 100% similarity to instantly claimed SEQ ID NO:4. The methods are both directed to identifying compounds that induce or inhibit the perception of a bitter taste as Zucker notes his method is for compounds that modulate (including compounds that induce, activate or inhibit). Both methods comprise contacting cells expressing TRP8 SEQ IDNO:4 (SEQ ID NO:8 of Zucker) with test compounds and measuring changes in signal transduction activation. Specifically Zucker notes the association of bitter taste with GPCR pathways such as cGMP, phosphodiesterase, phospholipase C, adenylate cyclase etc. with reference to paragraphs 9 and 10. Moreover, Zucker specifically notes the measurement and assessment of such levels including calcium ion concentration in cells in the presence or absence of test compound, see in particular Example II, p. 20. The specification associates such measurements with inducing or activating bitter stimuli as established via the discussion of the prior art (paragraphs 9-10) and inhibition or decreased levels of g protein transduction associated with inhbition of bitter stimuli. Consistent with Applicant's arguments of record with respect to the 112, 2nd paragraph rejection, the art establishes such suitable methods for assessing activation and inhibiton of TRP8. Thus, the reference teachings anticipate the claimed invention.

Status of Claims

17. No claims are allowed.

Conclusion

18. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

SHARON L. TURNER, PH.D.
PATENT EXAMINER

Sharon L. Turner, Ph.D.
September 29, 2004

9-29-04